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The application was originally filed in English.

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(21) *Patentansökningsnummer* / *Patent application number* — *0400044-4*

(86) *Ingivningsdatum* / *Date of filing* — *2004-01-12*

Stockholm, 2004-03-11

För Patent- och registreringsverket
For the Patent- and Registration Office

Hjördis Segerlund

Avgift
Fee 170:-

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FIELD OF THE INVENTION

The present invention relates to new compounds, to pharmaceutical formulations containing said compounds and to the use of said compounds in therapy. The present invention further relates to processes for the preparation of said compounds and to new intermediates used in the preparation thereof.

BACKGROUND OF THE INVENTION

Pain sensation in mammals is due to the activation of the peripheral terminals of a specialized population of sensory neurons known as nociceptors. Capsaicin, the active ingredient in hot peppers, produces sustained activation of nociceptors and also produces a dose-dependent pain sensation in humans. Cloning of the vanilloid receptor 1 (VR1 or TRPV1) demonstrated that VR1 is the molecular target for capsaicin and its analogues. (Caterina,M.J., Schumacher,M.A., et.al. Nature 1997 v.389 p 816-824). Functional studies using VR1 indicate that it is also activated by noxious heat and that the threshold for activation can be lowered below normal body temperature by a reduction of the extracellular pH value (acidification) and by other inflammatory mediators Tominaga,M., Caterina,M.J. et.al. Neuron 1998 v.21, p.531-543). Expression of VR1 is also regulated after peripheral nerve damage of the type that leads to neuropathic pain. These properties of VR1 make it a highly relevant target for pain and for diseases involving inflammation. Agonists of the VR1 receptor can act as analgesics, but the usefulness of agonists, such as capsaicin and its analogues, is limited by their pungency, neurotoxicity and induction of hypothermia. Pain-evoking stimuli activate the VR1 receptor and agents that block the activity of VR1 have also shown analgesic activity in animals.

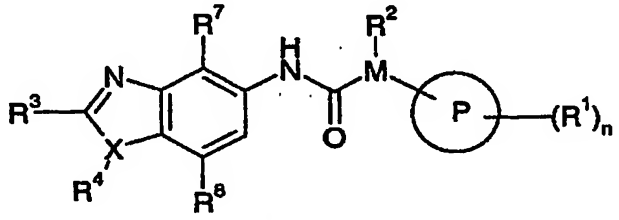
Compounds with VR1 blocker activity are believed to be of potential use for the treatment or prophylaxis of disorders such as pain, especially that of inflammatory or traumatic origin such as arthritis, fibromyalgia, low back pain and post-operative pain. (Walker et al J Pharmacol Exp Ther. 2003 Jan; 304(1):56-62), or visceral pains such as chronic pelvic pain, cystitis, irritable bowel syndrome (IBS), pancreatitis and the like, and also

neuropathic pain such as sciatia, diabetic neuropathy and HIV neuropathy, and the like (Walker et al *ibid*, Rashid et al J Pharmacol Exp Ther. 2003 Mar;304(3):940-8). These compounds are also believed to be potentially useful for inflammatory disorders like asthma, cough, inflammatory bowel disease (IBD) (Hwang and Oh Curr Opin Pharmacol 2002 Jun; 2(3):235-42). Compounds with VR1 blocker activity are also useful for itch and skin diseases like psoriasis and for gastro-esophageal reflux disease (GERD), emesis, urinary incontinence and hyperactive bladder (Yiangou et al BJU Int 2001 Jun; 87(9): 774-9, Szallasi Am J Clin Pathol 2002 118: 110-21). VR1 inhibitors are also of potential use for the treatment or prophylaxis of the effects of exposure to VR1 activators like capsaicin or tear gas, acids or heat (Szallasi *ibid*).

DETAILED DESCRIPTION OF THE INVENTION

The object of the present invention is to provide compounds exhibiting an activity at the vanilloid receptor 1 (VR1).

The present invention provides a compound of formula I



(I)

wherein:

ring P is C_{6-10}aryl, C_{3-7}cycloalkyl, C_{5-6}heteroaryl, whereby ring P may be fused with phenyl, C_{5-6}heteroaryl, C_{3-7}cycloalkyl or C_{3-7}heterocycloalkyl;

R^1 is H, NO_2, NH_2, halo, $N(C_{1-6}alkyl)_2$, C_{1-6}alkyl, C_{2-6}alkenyl, C_{2-6}alkynyl, C_{1-6}haloalkyl, C_{1-6}haloalkylO, phenylC_{0-6}alkyl, C_{5-6}heteroarylC_{0-6}alkyl, C_{3-7}cycloalkylC_{0-6}alkyl, C_{3-7}heterocycloalkylC_{0-6}alkyl, C_{1-6}alkylOC_{0-6}alkyl, C_{1-6}alkylSC_{0-6}alkyl or C_{1-6}alkylNC_{0-6}alkyl;

n is 0, 1, 2, 3 or 4;

M is H, C_{0-4}alkyl, C_{1-6}alkylNC_{0-6}alkyl, N or O;
R^2 is H or C_{0-4}alkyl;
R^3 is H, C_{1-6}alkyl, halo, C_{1-6}haloalkyl, C_{1-6}haloalkylO, C_{1-6}alkylOC_{0-6}alkyl, R^5OC_{1-6}alkyl, R^5CO, CO_2R^5, $CONR^5R^6$ or $NR^5R^6C_{0-6}$alkyl, C_{2-6}alkenylOC_{0-6}alkyl, hydroxyC_{1-6}alkyl;
X is N, O or S;
R^4 is H, C_{0-4}alkyl or hydroxyC_{1-6}alkyl;
R^5 and R^6 are independently selected from H, C_{1-6}alkyl, C_{5-6}aryl, C_{5-6}heteroaryl, SO_2C_{1-4}alkyl and COC_{1-3}alkyl;
R^7 and R^8 are independently selected from H, C_{1-6}alkyl, halo, C_{0-4}alkylcyano, C_{1-6}alkylOC_{0-6}alkyl, OH, NO_2, NH_2 andCO;
and wherein any alkyl, alkylOalkyl, haloalkyl, haloalkylO, phenyl, heteroaryl, cycloalkyl or heterocycloalkyl group may be substituted with one or more A; and
A is OH, NO_2, NH_2, CO, O(CO), halo, C_{1-6}alkylOC_{0-6}alkyl;
or salts, solvates or solvated salts thereof.

One embodiment of the invention relates to the compound of formula I wherein ring P is C_{6-10}aryl, C_{5-6}heteroaryl, ;
R^1 is H, halo, C_{1-6}alkyl, C_{1-6}haloalkyl, C_{1-6}alkylOC_{0-6}alkyl;
n is 0, 1 or 2;
R^3 is H, C_{1-6}alkyl, halo, C_{1-6}haloalkyl, C_{1-6}haloalkylO, C_{1-6}alkylOC_{0-6}alkyl, R^5OC_{1-6}alkyl, R^5CO, CO_2R^5, $CONR^5R^6$ or $NR^5R^6C_{0-6}$alkyl, C_{2-6}alkenylOC_{0-6}alkyl, hydroxyC_{1-6}alkyl;
X is N, O or S;
R^4 is H, C_{0-4}alkyl or hydroxyC_{1-6}alkyl;
R^5 and R^6 are independently selected from H, C_{1-6}alkyl, C_{5-6}aryl, C_{5-6}heteroaryl, SO_2C_{1-4}alkyl and COC_{1-3}alkyl;
R^7 and R^8 are independently selected from C_{0-4}alkylcyano;
and wherein any alkyl, alkylOalkyl, haloalkyl, haloalkylO, phenyl, heteroaryl, cycloalkyl or heterocycloalkyl group may be substituted with one or more A; and
A is OH, NO_2, halo, C_{1-6}alkylOC_{0-6}alkyl;
or salts, solvates or solvated salts thereof.

Another embodiment of the invention relates to the compound of formula I wherein ring P is phenyl or pyrazolyl.

In one embodiment of the invention R^1 is elected from the group consisting of is halo, C_{1-6}alkyl, C_{1-6}haloalkyl and C_{1-6}alkylOC_{0-6}alkyl and n is 0, 1, or 2.
Ring P may be substituted by R^1 on a nitrogen or carbon atom in ring P. Further, one atom on ring P may be substituted by two substituents R^1.

R^3 may be selected from the group consisting of H, C_{1-6}alkyl, halo, $CONR^5R^6$ or $NR^5R^6C_{0-6}$alkyl, C_{2-6}alkenylOC_{0-6}alkyl, hydroxyC_{1-6}alkyl whereby R^5 and R^6 are independently selected from H, C_{1-6}alkyl, C_{5-6}aryl, C_{5-6}heteroaryl, SO_2C_{1-4}alkyl and COC_{1-3}alkyl.
One embodiment of the invention relates to the compound of formula I wherein R^3 is hydroxymethyl, allyloxymethyl, ethoxymethyl, methoxypyridinylaminomethyl, pyrazolylaminomethyl, aminomethyl, methylsulfonylaminomethyl, acetylaminomethyl, carboxamide, methyl, hydroxyethyl, nitrophenylaminomethyl, hydroxycarbonyl or methoxycarbonyl.

R^4 may be selected from the group consisting of H, C_{0-4}alkyl or hydroxyC_{1-6}alkyl.

X may be selected from the group consisting of N, O and S. X may be substituted with R^4 when X is N. One embodiment of the invention relates to compounds of formula I wherein X is S.

Any alkyl, alkylOalkyl, haloalkyl, haloalkylO, phenyl, heteroaryl, cycloalkyl or heterocycloalkyl group present in the substituents of the compounds of formula I may be substituted with one or more A. One embodiment of the invention relates to compounds of formula I wherein A is selected from the group consisting of OH, NO_2, halo and C_{1-6}alkylOC_{0-6}alkyl.

Another embodiment of the invention relates to compounds selected from the group consisting of

4-tert-Butoxy-N-[2-(hydroxymethyl)-1,3-benzothiazol-5-yl]benzamide,
4-Bromo-N-[2-(hydroxymethyl)-1,3-benzothiazol-5-yl]benzamide,
N-[2-(Hydroxymethyl)-1,3-benzothiazol-5-yl]-4-iodobenzamide,
N-[2-(Hydroxymethyl)-1,3-benzothiazol-5-yl]-4-morpholin-4-ylbenzamide,
N-{2-[(Allyloxy)methyl]-1,3-benzothiazol-5-yl}-4-morpholin-4-ylbenzamide,
N-[2-(Hydroxymethyl)-1,3-benzothiazol-5-yl]-1-phenyl-5-propyl-1H-pyrazole-4-carboxamide,
1-tert-Butyl-N-[2-(hydroxymethyl)-1,3-benzothiazol-5-yl]-3-methyl-1H-pyrazole-5-carboxamide,
4-(Ethoxymethyl)-N-[2-(hydroxymethyl)-1,3-benzothiazol-5-yl]benzamide,
N-[2-(Hydroxymethyl)-1,3-benzothiazol-5-yl]-1-phenyl-1H-pyrazole-5-carboxamide,
4-Bromo-N-[2-(hydroxymethyl)-1,3-benzothiazol-5-yl]-2-methylbenzamide,
4-tert-Butoxy-N-(2-methyl-1,3-benzoxazol-5-yl) benzamide,
N-(4-Bromo-2-methyl-1,3-benzothiazol-5-yl)-4-tert-butylbenzamide,
4-tert-Butyl-N-(4,7-dibromo-2-methyl-1,3-benzothiazol-5-yl)benzamide,
N-[2-(hydroxymethyl)-1,3-benzothiazol-5-yl]-1-phenyl-5-(trifluoromethyl)-1H-pyrazole-4-carboxamide,
4-Iodo-N-(2-methyl-5-benzothiazolyl)benzamide,
4-(tert-Butoxymethyl)-N-[2-(hydroxymethyl)-1,3-benzothiazol-5-yl]benzamide,
N-(1,2-Dimethyl-1H-benzimidazol-5-yl)-4-iodobenzamide,
4-tert-Butyl-N-(2-{[(2-methoxypyridin-3-yl)amino]methyl}-1,3-benzothiazol-5-yl)benzamide,
4-tert-Butyl-N-[2-(1-hydroxyethyl)-1,3-benzothiazol-5-yl]benzamide,
4-tert-Butyl-N-{2-[(1H-pyrazol-3-ylamino)methyl]-1,3-benzothiazol-5-yl}benzamide,
4-(1,1-Dimethylethyl)-N-[2-[[(4-nitrophenyl)amino]methyl]-5-benzothiazolyl]-benzamide ,
N-[2-(Aminomethyl)-1,3-benzothiazol-5-yl]-4-tert-butylbenzamide,
4-tert-Butyl-N-(2-{[(methylsulfonyl)amino]methyl}-1,3-benzothiazol-5-yl)benzamide,
N-{2-[(Acetylamino)methyl]-1,3-benzothiazol-5-yl}-4-tert-butylbenzamide,
5-[(4-tert-Butylbenzoyl)amino]-1,3-benzothiazole-2-carboxamide,
N-1,3-Benzothiazol-5-yl-4-tert-butylbenzamide,
4-Chloro-N-[2-(hydroxymethyl)-1,3-benzothiazol-5-yl]benzamide,
1-(4-chlorophenyl)-N-[2-(hydroxymethyl)-1,3-benzothiazol-5-yl]-5-propyl-1H-pyrazole-4-carboxamide,

1-(4-chlorophenyl)-N-[2-(hydroxymethyl)-1,3-benzothiazol-5-yl]-5-(trifluoromethyl)-1H-pyrazole-4-carboxamide,
N-(2,4-dimethyl-1,3-benzothiazol-5-yl)-4-(1-hydroxy-1-methylethyl)benzamide,
4-(Hydroxymethyl)-N-[2-(hydroxymethyl)-1,3-benzothiazol-5-yl]benzamide and
4-tert-butyl-N-(4-cyano-2-methyl-1,3-benzothiazol-5-yl)benzamide,
or salts, solvates or solvated salts thereof.

Listed below are definitions of various terms used in the specification and claims to describe the present invention.

For the avoidance of doubt it is to be understood that where in this specification a group is qualified by 'hereinbefore defined', 'defined hereinbefore' or 'defined above' the said group encompasses the first occurring and broadest definition as well as each and all of the other definitions for that group.

For the avoidance of doubt it is to be understood that in this specification 'C_{1-6}' means a carbon group having 1, 2, 3, 4, 5 or 6 carbon atoms.

In this specification, unless stated otherwise, the term "alkyl" includes both straight and branched chain alkyl groups and may be, but are not limited to methyl, ethyl, n-propyl, i-propyl, n-butyl, i-butyl, s-butyl, t-butyl, n-pentyl, i-pentyl, t-pentyl, neo-pentyl, n-hexyl or i-hexyl, t-hexyl. The term C_{1-3} alkyl having 1 to 3 carbon atoms and may be methyl, ethyl, n-propyl, i-propyl or *tert*-butyl.

The term 'C_0' means a bond or does not excist. For example when M is C_0alkyl, M is a bond and "arylC_0alkyl" is equivalent with "aryl", "C_2aklylOC_0alkyl" is equivalent with "C_2alkylO".

In this specification, unless stated otherwise, the term "alkenyl" includes both straight and branched chain alkenyl groups. The term "C_{2-6}alkenyl" having 2 to 6 carbon atoms and one or two double bonds, may be, but is not limited to vinyl, allyl, propenyl, butenyl,

crotyl, pentenyl, or hexenyl, and a butenyl group may for example be buten-2-yl, buten-3-yl or buten-4-yl.

In this specification, unless stated otherwise, the term "alkynyl" includes both straight and branched chain alkynyl groups. The term "C_{2-6}alkynyl" having 2 to 6 carbon atoms and one or two trippel bonds, may be, but is not limited to etynyl, propargyl, pentynyl or hexynyl and a butynyl group may for example be butyn-3-yl or butyn-4-yl.

In this specification, unless stated otherwise, the term "cycloalkyl" refers to an optionally substituted, saturated cyclic hydrocarbon ring system. The term "C_{3-7}cycloalkyl" may be cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl or cycloheptyl.

The term "heterocycloalkyl" denotes a 3- to 7-membered, non-aromatic, partially or completely saturated hydrocarbon group, which contains one rings and at least one heteroatom. Examples of said heterocycle include, but are not limited to pyridyl, pyrrolyl, furyl, thienyl, imidazolyl, oxazolyl, isoxazolyl, thiazolyl, pyrazolyl, benzofuryl, indolyl, isoindolyl, benzimidazolyl, pyridazinyl, pyrimidinyl, pyrazinyl, tetrazolyl, triazolyl, pyrrolidinyl, pyrrolidonyl, piperidinyl, piperazinyl, morpholinyl, oxazolyl, 2-oxazolidonyl or tetrahydrofuranyl.

In this specification, unless stated otherwise, the term "aryl" refer to an optionally substituted monocyclic or bicyclic hydrocarbon unsaturated aromatic ring system. Examples of "aryl" may be, but are not limited to phenyl and naphthyl.

In this specification, unless stated otherwise, the term "heteroaryl" refer to an optionally substituted monocyclic or bicyclic unsaturated aromatic ring system containing at least one heteroatom selected independently form N, O or S. Examples of "heteroaryl" may be, but are not limited to pyridyl, pyrrolyl, furyl, thienyl, imidazolyl, oxazolyl, isoxazolyl, thiazolyl, pyrazolyl, benzofuryl, indolyl, isoindolyl, benzimidazolyl, pyridazinyl, pyrimidinyl, pyrazinyl, tetrazolyl, triazolyl and oxazolyl.

In this specification, unless stated otherwise, the term "arylalkyl" and "heteroarylalkyl" refer to a substituent that is attached via the alkyl or group to an aryl group.

In this specification, unless stated otherwise, the term "halo" and "halogen" may be fluoro, iodo, chloro or bromo.

In this specification, unless stated otherwise, the term "haloalkyl" means an alkyl group as defined above, which is substituted with halo as defined above. The term "C_{1-6}haloalkyl" may include, but is not limited to fluoromethyl, difluoromethyl, trifluoromethyl, fluoroethyl, difluoroethyl or bromopropyl. The term "C_{1-6}haloalkylO" may include, but is not limited to fluoromethoxy, difluoromethoxy, trifluoromethoxy, fluoroethoxy or difluoroethoxy.

The present invention relates to the compounds of formula I as hereinbefore defined as well as to the salts, solvates or solvated salts thereof. Salts for use in pharmaceutical formulations will be pharmaceutically acceptable salts, but other salts may be useful in the production of the compounds of formula I.

A suitable pharmaceutically acceptable salt of the compounds of the invention is, for example, an acid-addition salt, for example an inorganic or organic acid. In addition, a suitable pharmaceutically acceptable salt of the compounds of the invention is an alkali metal salt, an alkaline earth metal salt or a salt with an organic base.

Other pharmaceutically acceptable salts and methods of preparing these salts may be found in, for example, Remington's Pharmaceutical Sciences (18th Edition, Mack Publishing Co.).

Some compounds of formula I may have chiral centres and/or geometric isomeric centres (E- and Z- isomers), and it is to be understood that the invention encompasses all such optical, diastereoisomeric and geometric isomers.

The invention also relates to any and all tautomeric forms of the compounds of formula I.

Methods of Preparation

Another aspect of the present invention provides processes for preparing compounds of formula I, or salts, solvates or solvated salts thereof.

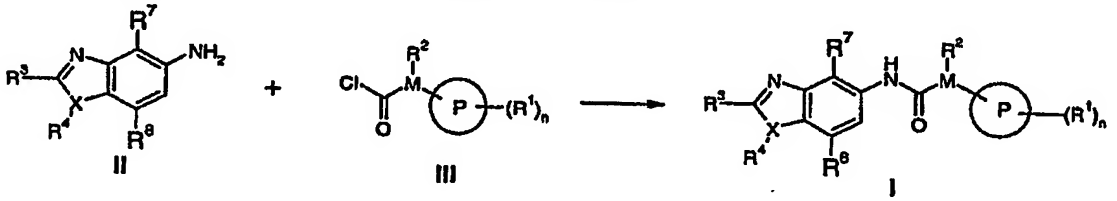
Throughout the following description of such processes it is to be understood that, where appropriate, suitable protecting groups will be added to, and subsequently removed from, the various reactants and intermediates in a manner that will be readily understood by one skilled in the art of organic synthesis. Conventional procedures for using such protecting groups as well as examples of suitable protecting groups are described, for example, in "Protective Groups in Organic Synthesis", T.W. Green, P.G.M. Wuts, Wiley-Interscience, New York, (1999). References and descriptions of other suitable reactions are described in textbooks of organic chemistry, for example, "Advanced Organic Chemistry", March, 4th ed. McGraw Hill (1992) or, "Organic Synthesis", Smith, McGraw Hill, (1994). For representative examples of heterocyclic chemistry see for example "Heterocyclic Chemistry", J. A. Joule, K. Mills, G. F. Smith, 3rd ed. Chapman and Hall (1995), p. 189-224 and "Heterocyclic Chemistry", T. L. Gilchrist, 2nd ed. Longman Scientific and Technical (1992), p. 248-282.

The term "room temperature" and "ambient temperature" shall mean, unless otherwise specified, a temperature between 16 and 25 °C.

One embodiment of the invention relates to processes for the preparation of the compound of formula I according to Methods A and B, wherein R^1 to R^8, unless otherwise specified, are defined as in formula I, comprising;

Compounds of formula (I) may be prepared by:

a) reaction of an aromatic amine of formula (II) with a properly substituted acyl chloride (III) optionally in the presence of a base:

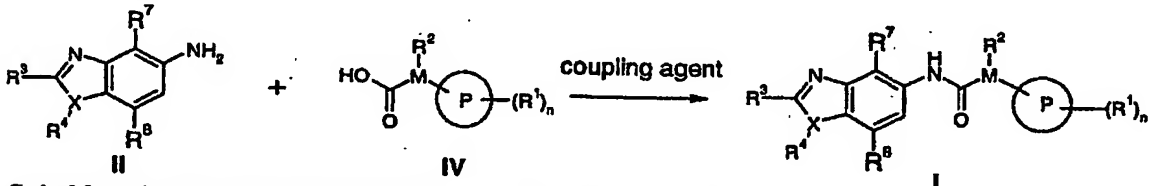


II + III → I

This reaction may be performed in any manner known to the skilled person in the art.

Suitable solvents to be used for this reaction may be halogenated hydrocarbons such as chloroform, dichloromethane and dichloroethane or aromatic and heteroaromatic compounds such as benzene, toluene, xylene, pyridine and lutidine or ethers such as ethyl ether, tetrahydrofuran and dioxan or any mixtures thereof. Catalysts such as heteroaromatic bases like pyridine and lutidine or tertiary amines like triethylamine, *N*-methylmorpholine and ethyl diisopropylamine may be used as well. The temperature may be between -40 and 40°C and the reaction time may be between 0.5 and 30 h.

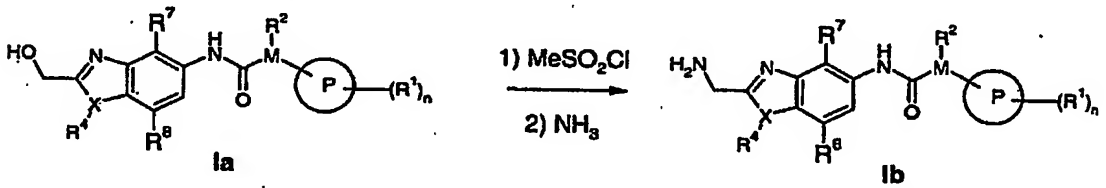
b) reaction of an aromatic amine of formula (II) with a properly substituted acid (IV) in the presence of a coupling agent (activator) like for example 1-[3-(dimethylamino)propyl]-3-ethylcarbodiimide hydrochloride.



II IV I

Suitable solvents to be used for this reaction may be tertiary amides such as dimethylformamide and dimethylacetamide, halogenated hydrocarbons such as chloroform, dichloromethane and dichloroethane or aromatic and heteroaromatic compounds such as benzene, toluene, xylene, pyridine and lutidine or ethers such as ethyl ether, tetrahydrofuran and dioxan or any mixtures thereof. Catalysts such as heteroaromatic bases like pyridine and lutidine or tertiary amines like triethylamine, *N*-methylmorpholine and ethyl diisopropylamine may be used as well. The temperature may be between 10 and 60°C and the reaction time may be between 3 and 30 h.

c) reaction of an hydroxymethyl derivative Ia with methanesulfonyl chloride followed by treatment with ammonia.

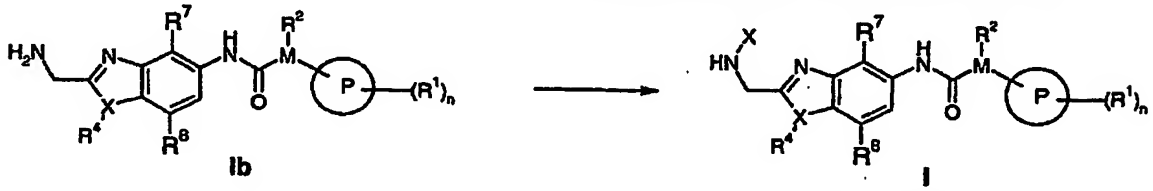


Ia Ib

The mesylation step is carried out using halogenated hydrocarbons such as chloroform, dichloromethane and dichloroethane as a solvent and a tertiary amine like triethylamine, *N*-methylmorpholine and ethyl diisopropylamine as a base in a temperature range between –

20 and 30 °C. The amination step step is carried out using a solution of ammonia in an alcohol like ethanol or in an aprotic solvent like dioxane or in water.

d) reaction of an aminomethyl derivative Ib with an acyl chloride or a sulfonyl chloride



Ib → I

X = acyl, sulfonyl

The reaction conditions are similar to the ones described for the mesylation step in part c).

e) oxidation of the aldehyde Ic to the corresponding carbonic acid followed by spontaneous decarboxylation

Ic → I

For the oxidation purpose a mixture of sodium chlorite and sulfamic acid in water may be employed

f) oxidation of the aldehyde Ic to the corresponding carbonic acid as in part e) followed by activation of the carbonic acid and amination as described in part b)

Ic → I

g) reduction of the aldehyde Ic to a corresponding primary alcohol

Ic → I

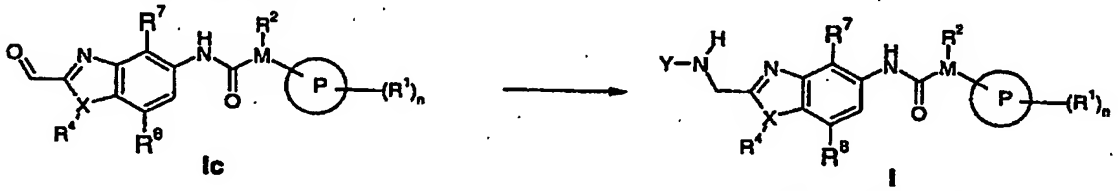
As a suitable reductive agent sodium borohydride may be used in a solvent like methanol or another alcohol or its mixture with water in a temperature range between -10 and 40°C

h) treatment of the aldehyde Ic with organometallic reagent leading to secondary alcohols

Ic I

Organometalic reagent may be a magnesium derivatives like methylmagnesium bromide or organolithium compound like methyllithium and a suitable solvent may be chosen from a range of aprotic inert solvents like diethyl ether, tetrahydrofuran, benzene, etc.

i) reductive amination of the aldehyde Ic

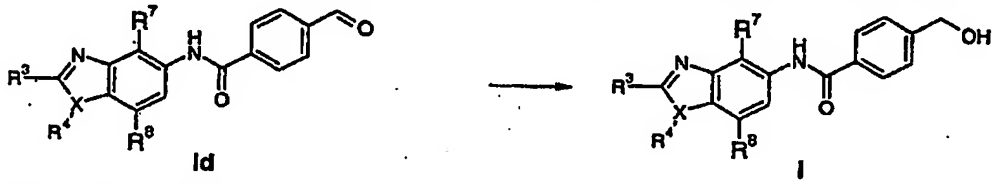


Ic I

Y is aryl, heteroaryl

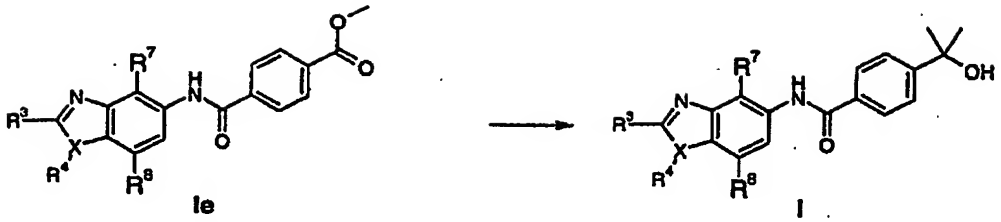
in process i) any primary amine may be used together with an appropriate reductive agent for example decaborane or sodium cyanoborohydride. Both protic and aprotic solvents, for example, alcohols, water, terahydrofuran and mixtures thereof are suitable and the temperature range is between 0 and 40°C.

j) reduction of the aldehyde Id to a corresponding primary alcohol as in part g)



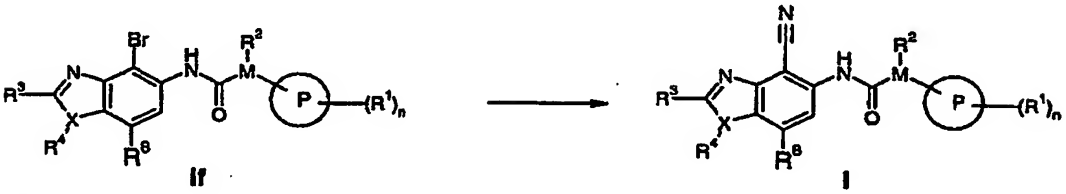
Id I

k) treatment of the methyl ester Ic with organometallic reagent leading to tertiary alcohols in a similar way to the process described in part h)



Ie I

l) reaction of the bromo derivative If with a cyanation reagent



If I

As a cyanation reagent copper (I) cyanide may be used in an aprotic polar solvent having high boiling point, like dimethyl formamide, at elevated temperature in a range between 150 and 270°C

Abbreviations

alloc	allyloxycarbonyl
DCE	dichloroethane
DCM	dichloromethane
DMAP	dimethylaminopyridine
EDC	1-(3-dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride
HATU	O-(7-azabenzotriazol-1-yl)-N,N,N',N'-tetramethyluronium hexafluorophosphate
HPLC	high performance liquid chromatography
LC	liquid chromatography
M	molar
MsCl	methanesulfonyl chloride
MS	mass spectometry
ret. time	retention time
TFA	trifluroacetic acid

A further embodiment of the invention relates to compounds

allyl (5-amino-1,3-benzothiazol-2-yl)methyl carbonate,
4-tert-Butyl-N-(2-formyl-1,3-benzothiazol-5-yl)-benzamide, and
4-Bromo-2-methyl-benzothiazol-5-ylamine,
which may be used as intermediates in the preparation of the compound of formula I.

Pharmaceutical formulation

According to one aspect of the present invention there is provided a pharmaceutical formulation comprising as active ingredient a therapeutically effective amount of the compound of formula I, or salts, solvates or solvated salts thereof, in association with one or more pharmaceutically acceptable diluents, excipients and/or inert carriers.

The composition may be in a form suitable for oral administration, for example as a tablet, pill, syrup, powder, granule or capsule, for parenteral injection (including intravenous, subcutaneous, intramuscular, intravascular or infusion) as a sterile solution, suspension or emulsion, for topical administration e.g. as an ointment, patch or cream or for rectal administration e.g. as a suppository.
In general the above compositions may be prepared in a conventional manner using one or more conventional excipients, pharmaceutical acceptable diluents and/or inert carriers.
Suitable daily doses of the compound of formula I in the treatment of a mammal, including man are approximately 0.01 to 250 mg/kg bodyweight at peroral administration and about 0.001 to 250 mg/kg bodyweight at parenteral administration. The typical daily dose of the active ingredients varies within a wide range and will depend on various factors such as the relevant indication, severity of the illness being treated, the route of administration, the age, weight and sex of the patient and the particular compound being used, and may be determined by a physician.

Medical use

Surprisingly, it has been found that the compounds according to the present invention are useful in therapy. The compounds of formula I, or salts, solvates or solvated salts thereof,

as well as their corresponding active metabolites, exhibit a high degree of potency and selectivity for individual vanilloid receptor 1 (VR1) groups. Accordingly, the compounds of the present invention are expected to be useful in the treatment of conditions associated with excitatory activation of vanilloid receptor 1 (VR1).

The compounds may be used to produce an inhibitory effect of VR1 in mammals, including man.

VR1 are highly expressed in the peripheral nervous system and in other tissues. Thus, it is expected that the compounds of the invention are well suited for the treatment of VR1 mediated disorders. The compounds of formula I are expected to be suited for the treatment of acute and chronic pain and acute and chronic inflammatory pain. The compound may further be suited for the treatment of chronic neuropathic pain.

Examples of such disorder may be selected from the group comprising of arthritis, fibromyalgia, low back pain, post-operative pain, visceral pains like chronic pelvic pain, cystitis, irritable bowel syndrome (IBS), pancreatitis, sciatia, diabetic neuropathy, HIV neuropathy, asthma, cough, inflammatory bowel disease (IBD) and psoriasis.

Further relevant disorders that may be treated using the compounds of formula I may be selected from the group comprising of gastro-esophageal reflux disease (GERD), emesis, urinary incontinence and hyperactive bladder.

The compounds of formula I may also be used as antitoxin to treat (over-) exposure to VR1 activators like capsaicin or tear gas, acids or heat.

The compounds may further be used for treatment of tolerance to VR1 activators.

One embodiment of the invention relates to the use of the compound of formula I in therapy.

Another embodiment of the invention relates to the use of the compound of formula I for treatment of VR1 mediated disorders.

A further embodiment of the invention relates to the use of the compound of formula I for treatment of acute and chronic pain disorders

Yet another embodiment of the invention relates to the use of the compound of formula I for treatment of acute and chronic inflammatory pain.

Yet a further embodiment of the invention relates to the use of the compound of formula I as hereinbefore defined, for treatment of indications selected form the group consisting of arthritis, fibromyalgia, low back pain, post-operative pain, visceral pains like chronic pelvic pain, cystitis, IBS, pancreatitis, sciatia, diabetic neuropathy, HIV neuropathy, asthma, cough, IBD, psoriasis, gastro-esophageal reflux disease (GERD), emesis, urinary incontinence and hyperactive bladder.

One embodiment of the invention relates to the use of the compound of formula I as hereinbefore defined, in the manufacture of a medicament for the treatment of VR1 mediated disorders and for the treatment of acute and chronic pain disorders and acute and chronic inflammatory pain and any other disorder mentioned above.

Another embodiment of the invention relates to a method of treatment of VR1 mediated disorders and acute and chronic pain disorders and acute and chronic inflammatory pain and any other disorder mentioned above, comprising administrering to a mammal, including man in need of such treatment, a therapeutically effective amount of the compound of formula I, as hereinbefore defined.

A further embodiment of the invention relates to a pharmaceutical formulation comprising the compound of formula I, as hereinbefore defined, for use in the treatment of VR1 mediated disorders and for the treatment of acute and chronic pain disorders and acute and chronic inflammatory pain and any other disorder mentioned above.

In the context of the present specification, the term "therapy" and "treatment" includes prevention and prophylaxis, unless there are specific indications to the contrary. The terms "treat","therapeutic" and "therapeutically" should be construed accordingly.

In this specification, unless stated otherwise, the term "antagonist" and "inhibitor" mean a compound that by any means, partly or completely, blocks the transduction pathway leading to the production of a response by the ligand.

The term "disorder", unless stated otherwise, means any condition and disease associated with vanilloid receptor activity.

Non- Medical use

In addition to their use in therapeutic medicine, the compounds of formula I, or salts, solvates or solvated salts thereof, are also useful as pharmacological tools in the development and standardisation of *in vitro* and *in vivo* test systems for the evaluation of the effects of inhibitors of VR1 related activity in laboratory animals such as cats, dogs, rabbits, monkeys, rats and mice, as part of the search for new therapeutics agents.

Examples

The invention will now be illustrated by the following non-limiting examples.

General methods

All starting materials are commercially available or described in the literature. The ^1H NMR spectra were recorded on Brucker at 400 MHz. The mass spectra were recorded utilising electrospray (LC-MS; LC:Waters 2790, column XTerra MS C_8 2.5 μm 2.1X30 mm, buffer gradient H_2O+0.1%TFA:CH_3CN+0.04%TFA, MS: micromass ZMD// ammonium acetate buffer) ionisation techniques.

Synthesis of aromatic amines as starting materials employed in amide bond-forming reactions in examples 1-17.

Allyl (5-amino-1,3-benzothiazol-2-yl)methyl carbonate

A. tert-Butyl (2-methyl-1,3-benzothiazol-5-yl)carbamate.

A mixture of Et_3N (8.00 mL), di-*tert*-butyl dicarbonate (7.01 g, 32.0 mmol) and 5-amino-2-methylbenzothiazole (2.63 g, 16.0 mmol) in MeOH (20.0 mL) was stirred at 55 °C for 1 hour ay room temperature for 18 hours. The mixture was concentrated under reduced pressure, and the residue was diluted with DCM. After washing with a 1M solution of HCl, the mixture was dried with Na_2SO_4, filtered and evaporated under reduced pressure to yield the carbamate derivative. MS [M+] calc. 264.0 found 264.9.

B. *tert*-Butyl [2-(hydroxymethyl)-1,3-benzothiazol-5-yl]carbamate.

A mixture of SeO_2 (4.44 g, 40.0 mmol) and the carbamate (Part A) (16.0 mmol) in dioxane (20.0 mL) was kept under a N_2 atmosphere and heated to 100 °C for 18 hours with vigorous stirring. After cooling to room temperature, the dioxane was removed by evaporation under reduced pressure. The residue was dissolved in EtOAc, washed with brine, dried with Na_2SO_4, filtered and concentrated under reduced pressure to yield the aldehyde. $R_f = 0.56$ (hexanes:EtOAc, 1:1). The aldehyde was dissolved in MeOH (20.0 mL) and $NaBH_4$ (1.51 g, 40.0 mmol) was added portion-wise. The mixture was stirred for 2 hours and then diluted with 1M NaOH. The MeOH was removed by evaporation, and the resulting residue was dissolved in EtOAc and washed with brine. The organic phase was collected, dried with Na_2SO_4, filtered and concentrated under reduced pressure to yield 1.83 g of the primary alcohol. MS [M+] calc. 280.0 found 280.9.

C. Allyl {5-[(*tert*-butoxycarbonyl)amino]-1,3-benzothiazol-2-yl}methyl carbonate.

The primary alcohol (part B) (1.70 g, 6.06 mmol) was dissolved in DCM (50.0 mL), and allylchloroformate (767 mg, 6.36 mmol) was added followed by DMAP (2.22 g, 18.2

mmol). The mixture was stirred for 3 hours, and the solvent was evaporated. The crude product was purified by flash chromatography on silica gel eluting with mixtures of hexanes and EtOAc (4:1, 2:1) to yield the alloc-protected derivative (1.943 g, 5.33 mmol, 88%). MS [M+] calc. 364.0 found 364.9.

D. Allyl (5-amino-1,3-benzothiazol-2-yl)methyl carbonate.

The alloc-protected derivative (part C) (1.90 g, 5.22 mmol) was dissolved in DCM (20.0 mL), and TFA (3.00 mL) was added. The mixture was stirred for 4 hours, and then concentrated under reduced pressure to yield a light brown powder, which was used in the subsequent coupling reactions without further purification. ^{1}H NMR (400 MHz, CHLOROFORM-D) δ ppm 4.71 (d, *J*=5.86 Hz, 2 H) 5.30 (dd, *J*=10.35, 1.17 Hz, 1 H) 5.37 (q, *J*=3.0, 1.50 Hz, 1 H) 5.42 (q, *J*=3.0, 1.50 Hz, 1 H) 5.51 (s, 2 H) 5.95 (m, 1 H) 7.10 (s, 1 H) 7.63 (s, 1 H) 7.70 (d, *J*=8.01 Hz, 1 H); MS [M+] calc. 264.0 found 264.8.

4-Bromo-2-methyl-1,3-benzothiazol-5-ylamine and 4,6-Dibromo-2-methyl-benzothiazol-5-ylamine

5-Amino-2-methylbenzothiazole (2.45 g, 14.9 mmol) and Br_2 (2.38 g, 14.9 mmol) were mixed in $CHCl_3$ (60.0 mL) and stirred for 45 minutes. 28% NH_4OH (20.0 mL) was added, and the aqueous phase was extracted with DCM. The combined organic phases were dried with $MgSO_4$, filtered and evaporated. The products were separated from by flash chromatography on silica gel eluting with mixtures of hexanes and EtOAc (4:1) to yield 4-bromo-2-methyl-1,3-benzothiazol-5-ylamine: LC ret. time 1.13 minutes (Column: Phenomonex Polar, Gradient: 10-95% B, Flow rate:1.75 mL/min, Column temperature: 40 °C, Mobile phase: A - 0.1% TFA in H_2O, B - 0.1% TFA in MeCN), MS [M+] calcd. 242.0, found 242.0; and 4,6-dibromo-2-methyl-benzothiazol-5-ylamine: LC ret. time 1.64 minutes MS [M+] calcd. 322.0, found 322.0

Example 1

4-*tert*-Butoxy-*N*-[2-(hydroxymethyl)-1,3-benzothiazol-5-yl]benzamide.

A. Synthesis of the O-alloc protected derivative

Allyl (5-amino-1,3-benzothiazol-2-yl)methyl carbonate (see above) (97.0 mg, 0.370 mmol) and 4-*tert*-butoxybenzoic acid (71.0 mg, 0.370 mmol) were mixed in a mixture of DCM (5.00 mL) and DMF (5.00 mL) with EDC (220 mg, 1.15 mmol) and DMAP (236 mg, 1.15 mmol).). The mixture was stirred for 18 hours, and the solvents were evaporated. The residue was dissolved in DCM and washed with a saturated solution of $NaHCO_3$. The mixture was dried with Na_2SO_4, filtered and concentrated under reduced pressure. The crude product was purified by Gilson reverse phase HPLC (Luna 15 u, C18 (2) 250 mm X 21.2 mm), eluting with mixtures of H_20 and MeCN with 0.1% TFA the O-alloc protected derivative of the title compound: MS [M+] calc. 440.0 found 440.9.

B. Deprotection

The product obtained in Part A was treated with a solution of $Pd(OAc)_2$ (10.0 mg), PPh_3 (20.0 mg) and Et_3SiH (176 mg, 1.52 mmol, 0.240 mL) in a mixture of THF (4.00 mL) and DMF (4.00 mL). The mixture was stirred at room temperature until the reaction appeared complete by TLC analysis, and the solvents were evaporated. The crude product was purified by Gilson HPLC (Luna 15 u, C18 (2), 250 mm X 21.2 mm) eluting with mixture of MeCN and H_2O containing 1%TFA to yield the title product. ^1H NMR (400 MHz, METHANOL-D4) δ ppm 1.42 (s, 9 H) 4.95 (s, 2 H) 7.12 (m, 2 H) 7.71 (dd, J=8.79, 1.17 Hz, 1 H) 7.91 (m, 2 H) 7.96 (d, J=8.79 Hz, 1 H) 8.40 (s, 1 H); MS [M+H] calc. 357.1 found 357.0; Anal. found C 64.61% H 5.58% N 6.65%.

Example 2

4-Bromo-*N*-[2-(hydroxymethyl)-1,3-benzothiazol-5-yl]benzamide.

4-Bromobenzoylchloride (0.4 mmol) was dissolved in DCM and DMAP (0.4 mmol) was added. The mixture was stirred for 10 minutes and then allyl (5-amino-1,3-benzothiazol-2-yl)methyl carbonate (100 mg, 0.38 mmol) was added. The mixture was stirred until the

reaction appeared complete by TLC analysis and NaOH (1M) was added. The aqueous phase was extracted with DCM. The organic phases were collected, dried with Na_2SO_4, filtered and concentrated under reduced pressure. Purification by HPLC afforded the O-alloc protected derivative of the title compound: MS [M+1] calc. 448.0 found 448.4. Deprotection according to the procedure described in Example 1, part B afforded the title compound; δ ppm 4.79 (s, 2H) 7.55 (d, J=8.3 Hz, 3 H) 7.74 (d, J=8.4 Hz, 2 H) 7.80 (d, J=8.7 Hz, 1 H) 8.25 (s, 1 H); MS [M+H] calc. 363.2 found 363.0.

Compounds in the following examples were synthesized according to the amide bond-forming procedures described in the examples 1 or 2 starting from an appropriate aromatic amine, either commercially available or synthesized according to the procedures described above, and an appropriately substituted commercially available aromatic acid or an aromatic acyl chroride. Where appropriate the amide bond-forming procedures were followed by the deprotection as described in Example 1

Example number	Name	MW calcd	MW found [M+1]	^{1}H NMR
3	***N*-[2-(Hydroxymethyl)-1,3-benzothiazol-5-yl]-4-iodobenzamide**	411.1	411.0	(600 MHz, CD^3OD) δppm 4.79 (s, 2H) 7.55 (d, J=8.3 Hz, 3 H) 7.74 (d, J=8.4 Hz, 2 H) 7.80 (d, J=8.7 Hz, 1 H) 8.25 (s, 1 H)
4	**N-[2-(Hydroxymethyl)-1,3-benzothiazol-5-yl]-4-morpholin-4-ylbenzamide**	370.1	370.0	(400 MHz, DMSO-D_6) δ ppm 3.24 (m, 4 H), 3.73 (m, 4 H) 4.83 (d, J=6.05 Hz, 2 H) 6.22 (t, J=5.96 Hz, 1 H) 7.02 (d, J=9.18 Hz, 2 H) 7.76 (dd, J=8.69, 2.05 Hz, 1 H) 7.90 (d, J=9.18 Hz, 2 H) 7.98 (d, J=8.79 Hz, 1 H) 8.42 (d,

				J=1.95 Hz, 1 H) 10.13 (s, 1 H)
5 (no deprotection step required)	**N-{2-[(Allyloxy)methyl]-1,3-benzothiazol-5-yl}-4-morpholin-4-ylbenzamide**	410.2	410.0	(400 MHz, METHANOL-D_4) δ ppm 3.09 (m, 4 H), 3.73 (m, 4 H) 4.58 (d, J=6.05 Hz, 2 H) 4.90 (s, 2 H) 5.16 (m, 2 H) 5.99 (m, 1 H) 6.70 (m, 2 H) 7.22 (m, 3 H) 7.62 (d, J=1.95 Hz, 1 H) 7.87 (d, J=8.59 Hz, 1 H)
6	**N-[2-(Hydroxymethyl)-1,3-benzothiazol-5-yl]-1-phenyl-5-propyl-1H-pyrazole-4-carboxamide**	393.1	392.9	(400 MHz, METHANOL-D_4) δ ppm 3.09 (m, 4 H), 3.73 (m, 4 H) 4.58 (d, J=6.05 Hz, 2 H) 4.90 (s, 2 H) 5.16 (m, 2 H) 5.99 (m, 1 H) 6.70 (m, 2 H) 7.22 (m, 3 H) 7.62 (d, J=1.95 Hz, 1 H) 7.87 (d, J=8.59 Hz, 1 H)
7	**1-tert-Butyl-N-[2-(hydroxymethyl)-1,3-benzothiazol-5-yl]-3-methyl-1H-pyrazole-5-carboxamide**	345.1	345.0	(400 MHz, METHANOL-D_4) δ ppm 1.71 (s, 9 H) 2.52 (s, 3 H) 4.95 (s, 2 H) 6.61 (s, 1 H) 7.69 (dd, J=8.69, 1.85 Hz, 1 H) 7.93 (d, J=8.79 Hz, 1 H) 8.43 (d, J=1.95 Hz, 1 H)
8	**4-(Ethoxymethyl)-N-[2-(hydroxymethyl)-1,3-benzothiazol-5-yl]benzamide**	343.1	343.0	(400 MHz, METHANOL-D_4) δ ppm 1.24 (t, J=7.03 Hz, 3 H) 3.58 (q, J=7.03 Hz, 2 H) 4.58 (s, 2 H) 4.95 (s, 2 H) 7.48 (d, J=8.59 Hz, 2 H) 7.71 (dd, J=8.69, 2.05 Hz, 1 H) 7.92 (s, 1 H) 7.94 (d, J=7.81 Hz, 2 H) 8.41 (d, J=1.95 Hz, 1 H)

9	N-[2-(Hydroxymethyl)-1,3-benzothiazol-5-yl]-1-phenyl-1H-pyrazole-5-carboxamide	335.1	335.0	(400 MHz, CHLOROFORM-D) δ ppm 2.78 (s, 3 H) 6.79 (d, J=1.76 Hz, 1 H) 7.35 (m, 5 H) 7.60 (m, 3 H) 7.89 (s, 1 H)
10	4-Bromo-*N*-[2-(hydroxymethyl)-1,3-benzothiazol-5-yl]-2-methylbenzamide	377.0	377.0	(400 MHz, METHANOL-D_4) δ ppm 2.45 (s, 3 H) 4.95 (s, 2 H) 7.40 (d, J=8.20 Hz, 1 H) 7.45 (m, 1 H) 7.49 (s, 1 H) 7.66 (dd, J=8.69, 2.05 Hz, 1 H) 7.93 (d, J=8.59 Hz, 1 H) 8.40 (d, J=1.95 Hz, 1 H)
11	4-tert-Butoxy-N-(2-methyl-1,3-benzoxazol-5-yl) benzamide	325.1	325.2	(400 MHz, CHLOROFORM-D) δppm 1.41 (s, 9 H) 2.63 (s, 3 H) 7.07 (m, 2 H) 7.43 (d, J=8.79 Hz, 1 H) 7.58 (dt, J=8.79, 2.15 Hz, 1 H) 7.82 (m, 2 H) 7.89 (d, J=1.95 Hz, 1 H) 7.98 (s, 1 H)
12	N-(4-Bromo-2-methyl-1,3-benzothiazol-5-yl)-4-tert-butylbenzamide	403.0	403.0	(400 MHz, CHLOROFORM-D) δ ppm 1.38 (s, 9 H) 2.90 (s, 3 H) 7.56 (d, J=8.59 Hz, 2 H) 7.79 (d, J=8.79 Hz, 1 H) 7.93 (d, J=8.59 Hz, 2 H) 8.63 (d, J=8.98 Hz, 1 H)
13	4-*tert*-Butyl-*N*-(4,7-dibromo-2-methyl-1,3-benzothiazol-5-yl)benzamide	481.0	480.7	(400 MHz, METHANOL-D_4) δ ppm 1.37 (s, 9 H) 2.85 (s, 3 H) 7.58 (d, J=8.40 Hz, 2 H) 7.97 (d, J=8.40 Hz, 2 H) 8.31 (s, 1 H)
14	*N*-[2-(hydroxymethyl)-1,3-benzothiazol-5-yl]-1-	419.1	419.0	(400 MHz, METHANOL-D4) δ ppm 4.95 (m, 2 H), 7.59 (m,

	phenyl-5-(trifluoromethyl)-1*H*-pyrazole-4-carboxamide			6 H), 7.96 (m, 1 H), 8.14 (m, 1 H), 8.37 (m, 1 H).
15	**4-Iodo-*N*-(2-methyl-5-benzothiazolyl)benzamide**	395.0	394.8	(400 MHz, CHLOROFORM-D) δ ppm 2.84 (s, 3 H) 7.64 (d, *J*=8.59 Hz, 2 H) 7.73 (dd, *J*=8.59, 1.95 Hz, 1 H) 7.80 (m, 1 H) 7.86 (d, *J*=8.59 Hz, 2 H) 7.94 (m, 1 H) 8.14 (d, *J*=1.95 Hz, 1 H)
16	**4-(*tert*-Butoxymethyl)-*N*-[2-(hydroxymethyl)-1,3-benzothiazol-5-yl]benzamide**	371.1	371.0	(400 MHz, METHANOL-D_4) δ ppm 1.30 (s, 9 H) 4.54 (s, 2 H) 4.94 (s, 2 H) 7.48 (d, J=8.59 Hz, 2 H) 7.71 (dd, J=8.69, 2.05 Hz, 1 H) 7.92 (m, 3 H) 8.39 (d, J=1.56 Hz, 1 H)
17	***N*-(1,2-Dimethyl-1*H*-benzimidazol-5-yl)-4-iodobenzamide**	392.0	392.0	(400 MHz, DMSO-D_6) δ ppm 2.75 (s, 3 H) 3.87 (s, 3 H) 7.75 (d, J=8.59 Hz, 2 H) 7.80 (t, J=2.05 Hz, 1 H) 7.84 (d, J=8.98 Hz, 1 H) 7.92 (d, J=8.40 Hz, 2 H) 8.32 (t, J=2.15 Hz, 1 H) 10.58 (s, 1 H)

Example 18

4-tert-Butyl-N-(2-{[(2-methoxypyridin-3-yl)amino]methyl}-1,3-benzothiazol-5-yl)benzamide.

A mixture of SeO_2 (4.44 g, 40.0 mmol) and 4-tert-butyl-N-(2-methyl-benzothiazol-5-yl)-benzamide (16.0 mmol) in dioxane (20.0 mL) was kept under a N_2 atmosphere and heated to 100 °C for 18 hours with vigorous stirring. After cooling to room temperature, the

dioxane was removed by evaporation under reduced pressure. The resulting residue was dissolved in EtOAc, washed with brine, dried with Na_2SO_4, filtered and concentrated under reduced pressure to yield the aldehyde, MS (ESI^+) *m/z* 325.0 $[M+H]^+$. The aldehyde (100 mg, 0.300 mmol) was mixed with 2-methoxypyridin-3-amine (36.0 mg, 0.300 mmol) and $MgSO_4$ (100 mg) in THF (3.00 mL). After 18 hours, $B_{10}H_4$ (14.0 mg, 0.320 mmol) dissolved in MeOH (3.00 mL) was added. The mixture was stirred until the reaction appeared complete by TLC analysis. 1M NaOH was added and the solvents were evaporated. The residue was purified by flash chromatography eluting with mixtures of hexanes and EtOAc (4:1, 1:1). ^1H NMR (400 MHz, CHLOROFORM-D) δ ppm 1.29 (s, 9 H) 3.98 (s, 3 H) 4.68 (d, J=5.86 Hz, 2 H) 6.67 (m, 2 H) 7.40 (dt, J=8.69, 2.10 Hz, 2 H) 7.51 (dd, J=4.69, 1.95 Hz, 1 H) 7.66 (d, J=1.17 Hz, 2 H) 7.80 (ddd, J=8.59, 2.25, 2.05 Hz, 2 H) 8.25 (d, J=1.17 Hz, 1 H) 8.45 (s, 1 H); MS [M+H] calc. 447.2 found 447.0.

Example 19

4-*tert*-Butyl-*N*-[2-(1-hydroxyethyl)-1,3-benzothiazol-5-yl]benzamide

Methylmagnesium bromide (276 uL, 3.0 M in Et_2O) was added dropwise via syringe to a stirred solution of the aldehyde (obtained as an intermediate in Example 18) (100 mg, 0.30 mmol) in THF (10.0 mL) at -78°C under nitrogen. After addition was complete the mixture was stirred for additional 1 hour and quenched with saturated aqueous ammonium chloride (2.0 mL). The mixture was diluted with EtOAc (25.0 mL) and water (20.0 mL) and the organic phase was seaprated. The aqueous phase was extracted with EtOAc (2 X 10.0 mL) and the organic phases combined and washed with brine solution (30.0 mL). The organic was dried with Na_2SO_4, filtered and concentrated by rotary evaporator to a residue which was purified by column chromatography on silica gel using EtOAc/hexanes as an eluent to yield the title product. ^1H NMR (400 MHz, METHANOL-D4) δ ppm 1.34 (s, 9 H), 1.62 (d, J=6.44 Hz, 3 H), 5.12 (m, 1 H), 7.54 (d, J=8.59 Hz, 2 H), 7.69 (dd, J=8.69, 2.05 Hz, 1 H), 7.89 (m, 3 H), 8.39 (d, J=1.95 Hz, 1 H). MS [M+H] calc. 355.1 found 355.2.

Example 20

4-tert-Butyl-N-{2-[(1H-pyrazol-3-ylamino)methyl]-1,3-benzothiazol-5-yl}benzamide

The title compounds wa synthesized according to the procedure described in Example 18 using 1*H*-pyrazol-3-amine at the reductive amination step. ^{1}H NMR (400 MHz, METHANOL-D4) δ ppm 1.31 (m, 9 H) 4.71 (s, 2 H) 5.62 (d, J=2.34 Hz, 1 H) 7.35 (d, J=2.34 Hz, 1 H) 7.53 (d, J=8.79 Hz, 2 H) 7.67 (dd, J=8.69, 2.05 Hz, 1 H) 7.83 (d, J=8.59 Hz, 1 H) 7.88 (d, J=8.79 Hz, 2 H) 8.37 (d, J=1.76 Hz, 1 H); MS [M+H] calc. 406.2 found 406.0.

Example 21

4-(1,1-Dimethylethyl)-*N*-[2-[[(4-nitrophenyl)amino]methyl]-5-benzothiazolyl]-benzamide

The title compounds wa synthesized according to the procedure described in Example 18 using p-nitroaniline at the reductive amination step. ^{1}H NMR (400 MHz, DMSO-D6) δ ppm 1.32 (s, 9 H), 4.91 (m, 2 H), 6.78 (d, J=9.18 Hz, 2 H), 7.56 (d, J=8.40 Hz, 2 H), 7.76 (dd, J=8.79, 1.95 Hz, 1 H), 7.91 (d, J=8.40 Hz, 2 H), 7.97 (d, J=8.79 Hz, 1 H), 8.02 (d, J=9.18 Hz, 2 H), 8.17 (t, J=6.25 Hz, 1 H), 8.50 (d, J=1.76 Hz, 1 H), 10.38 (s, 1 H). MS [M+H] calc. 461.2 found 461.0.

Example 22

N-[2-(Aminomethyl)-1,3-benzothiazol-5-yl]-4-*tert*-butylbenzamide

4-tert-Butyl-N-(2-hydroxymethyl-benzthiazol-5-yl)-benzamide (44.0 mg, 0.380 mmol) was mixed with MsCl (40.0 mg, 0.390 mmol, 0.0540 mL) and Et_3N (51.0 mg, 0.500 mmol) in DCM (5.00 mL) and the solution was stirred for 10 minutes. NH_3 (2.0M in EtOH) was added, and the mixture was stirred for additional 18 hours. The solvent was evaporated, and the crude product was purified by HPLC (Luna 15 u, C18 (2), 250 mm X 21.2 mm) eluting with mixtures of MeCN and H_2O containing 1%TFA. ^{1}H NMR (400 MHz, METHANOL-D4) δ ppm 1.21 (s, 9 H) 4.48 (s, 2 H) 7.41 (d, J=8.20 Hz, 2 H) 7.57

(d, J=8.20 Hz, 1 H) 7.76 (d, J=8.20 Hz, 2 H) 7.83 (d, J=8.59 Hz, 1 H) 8.47 (s, 1 H); MS [M+H] calc. 340.1 found 340.3.

Example 23

4-*tert*-Butyl-*N*-(2-{[(methylsulfonyl)amino]methyl}-1,3-benzothiazol-5-yl)benzamide

N-[2-(Aminomethyl)-1,3-benzothiazol-5-yl]-4-*tert*-butylbenzamide (example 22) (130 mg, 0.384 mmol) was stirred with MsCl (44.0 mg, 0.387 mmol) and Et_3N (58.0 mg, 0.600 mmol, 0.0800 mL) in DCM (5.00 mL) for 1 hour. The solvent was evaporated, and the residue was purified by HPLC (Luna 15 u, C18 (2), 250 mm X 21.2 mm) eluting with mixtures of MeCN and H_2O containing 1%TFA to yield the title product. ^1H NMR (400 MHz, CHLOROFORM-D) δ ppm 1.35 (s, 9 H) 3.05 (s, 3 H) 4.79 (s, 2 H) 5.73 (s, 1 H) 7.52 (d, J=8.59 Hz, 2 H) 7.80 (s, 2 H) 7.85 (d, J=8.40 Hz, 2 H) 8.12 (s, 1 H) 8.23 (s, 1 H); MS [M+] calc. 417.5 found 417.9; Anal. found C 54.39% H 5.43% N 8.71%.

Example 24

N-{2-[(Acetylamino)methyl]-1,3-benzothiazol-5-yl}-4-*tert*-butylbenzamide

N-[2-(Aminomethyl)-1,3-benzothiazol-5-yl]-4-*tert*-butylbenzamide (example 22) (60.0 mg, 0.18 mmol) was stirred with acetyl chloride (16.0 mg, 0.2 mmol, 0.015 mL) and Et_3N (25.0 mg, 0.25 mmol) in DCM (5.00 mL) for 1 hour. The solvent was evaporated, and the residue was purified by HPLC eluting with mixtures of MeCN and H_2O containing 1% TFA to yield the title product. ^1H NMR (400 MHz, CHLOROFORM-D) δ ppm 1.35 (s, 9 H) 2.12 (s, 3 H) 4.84 (s, 2 H) 7.49 (d, J=8.40 Hz, 2 H) 7.68 (s, 1 H) 7.75 (d, J=8.79 Hz, 1 H) 7.84 (d, J=8.20 Hz, 2 H) 8.20 (s, 1 H) 8.64 (s, 1 H) 11.35 (s, 1 H); MS [M+H] calc. 382.1 found 382.0; Anal. found C 55.85% H 4.94% N 8.60%.

Example 25

5-[(4-tert-Butylbenzoyl)amino]-1,3-benzothiazole-2-carboxamide

The aldehyde (example 18) (100 mg, 0.3 mmol) was dissolved in THF (10.0 mL) and a mixture of sodium chlorite (54.0 mg, 0.6 mmol) and sulfamic acid (58.0 mg, 0.6 mmol) in H_2O (5.0 mL) was added drop-wise. The mixture was stirred for 1 hour, and then the aqueous phase was extracted with EtOAc. The combined organic phases were dried over $MgSO_4$, filtered and evaporated to yield the acid, which was immediately dissolved in DCM (5.0 mL) containing a mixture of allyl chloroformate (48.0 mg, 0.400 mmol) and DMAP (48.0 mg, 0.400 mmol, 0.340 mL). The mixture was stirred for 1 hour and then evaporated to yield the mixed anhydride: MS [M+] calc. 435.0 found 435.9. The anhydride was dissolved in 5.0 mL of EtOH containing NH_3 (2.0M), and the mixture was stirred for 18 hours. The solvent was evaporated, and the product was purified by flash chromatography eluting with mixtures of hexanes and EtOAc (4:1, 1:1) to yield decarboxylated material (see below, example 25) and the title product. ^{1}H NMR (400 MHz, CHLOROFORM-D) δ ppm 1.34 (m, 9 H) 6.11 (s, 2 H) 7.41 (s, 1 H) 7.49 (d, J=7.62 Hz, 2 H) 7.73 (d, J=8.59 Hz, 1 H) 7.86 (d, J=7.23 Hz, 2 H) 8.33 (m, 1 H) 8.49 (s, 1 H); MS [M+H] calc. 354.1 found 354.0.

Example 26

N-1,3-Benzothiazol-5-yl-4-tert-butylbenzamide

See above (example 24). ^{1}H NMR (400 MHz, DMSO-D_6) δ ppm 1.30 (s, 9 H) 7.54 (d, J=8.40 Hz, 2 H) 7.82 (dd, J=8.79, 1.95 Hz, 1 H) 7.90 (d, J=8.59 Hz, 2 H) 8.08 (d, J=8.79 Hz, 1 H) 8.59 (d, J=1.95 Hz, 1 H) 9.36 (s, 1H) 10.38 (s, 1 H); IR (neat) 1661 cm^{-1}; MS [M+H] calc. 311.1 found 311.0.

Example 27

4-Chloro-*N*-[2-(hydroxymethyl)-1,3-benzothiazol-5-yl]benzamide

According to amide bond forming procedure described in Example 2, 5-amino-2-methylbenzothiazole reacted with 4-chlorobenzoyl chloride to yield 4-chloro-N-(2-methyl-

benzothiazol-5-yl)-benzamide: MS [M+] calc. 302, found 302.0. This intermediate was oxidized with SeO_2 to the corresponding aldehyde as described in Example 18. The aldehyde (3.30 mmol) was mixed with $NaBH_4$ (122 mg, 3.30 mmol) in MeOH (150 mL). After the reaction was complete according to TLC, the volatiles were removed and the residue was dissolved in a mixture of DCM and MeOH (10 mL, 1:5) and passed through a short pad of silica. The filtrate was concentrated and a residue was crystallized from a mixture of EtOAc and MeOH (40:1). A yellow solid formed was collected by filtration. ^{1}H NMR (400 MHz, DMSO-D6) δ ppm 4.85 (m, 2 H), 6.26 (t, J=5.96 Hz, 1 H), 7.62 (d, J=8.40 Hz, 2 H), 7.76 (m, 1 H), 8.02 (m, 3 H), 8.43 (m, 1 H), 10.50 (s, 1 H). MS [M+H] calc. 319.0 found 319.0.

Example 28

1-(4-chlorophenyl)-*N*-[2-(hydroxymethyl)-1,3-benzothiazol-5-yl]-5-propyl-1*H*-pyrazole-4-carboxamide

The title compound was synthesized from 5-amino-2-methylbenzothiazole and 1-(4-chlorophenyl)-5-propyl-1*H*-pyrazole-4-carbonyl chloride according to the procedure described in the example 27. ^{1}H NMR (400 MHz, DMSO-D6) δ ppm 0.76 (t, J=7.32 Hz, 3 H), 1.46 (m, 2 H), 2.97 (m, 2 H), 4.85 (d, J=6.05 Hz, 2 H), 6.26 (t, J=5.96 Hz, 1 H), 7.55 (d, J=8.79 Hz, 2 H), 7.65 (d, J=8.79 Hz, 2 H), 7.74 (dd, J=8.79, 1.95 Hz, 1 H), 8.01 (d, J=8.59 Hz, 1 H), 8.36 (m, 2 H), 10.07 (s, 1 H). MS [M+H] calc. 427.1 found 427.0.

Example 29

1-(4-chlorophenyl)-*N*-[2-(hydroxymethyl)-1,3-benzothiazol-5-yl]-5-(trifluoromethyl)-1*H*-pyrazole-4-carboxamide

The title compound was synthesized from 5-amino-2-methylbenzothiazole and 1-(4-chlorophenyl)-5-(trifluoromethyl)-1*H*-pyrazole-4-carbonyl chloride according to the procedure described in the example 27. ^{1}H NMR (400 MHz, DMSO-D6) δ ppm 4.86 (d, J=6.05 Hz, 2 H), 6.26 (t, J=5.96 Hz, 1 H), 7.60 (d, J=8.59 Hz, 2 H), 7.69 (m, 3 H), 8.04 (d,

J=8.59 Hz, 1 H), 8.37 (m, J=4.69 Hz, 2 H), 10.72 (s, 1 H). MS [M+H] calc. 453.0 found 452.9.

Example 30

N-(2,4-dimethyl-1,3-benzothiazol-5-yl)-4-(1-hydroxy-1-methylethyl)benzamide.

According to amide bond forming procedure described in Example 1, 5-amino-2-methylbenzothiazole reacted with 4-(methoxycarbonyl)benzoic acid to yield N-(2-Methyl-benzothiazol-5-yl)-terephthalamic acid methyl ester: MS [M+] calc. 326.0, found 326.0. This intermediate was placed into a flask, which was capped with a rubber septum and charged with N_2 gas. THF (10.0 mL) was added, followed by MeMgBr (4.60 mmol, 1.53 mL), and the reaction was stirred for 8 hours at room temperature. A saturated solution of NH_4Cl was added, and the mixture was evaporated to dryness in vacuum. The residue was purified by HPLC eluting with mixtures of MeCN and H_2O containing 1%TFA to yield the title product. ^1H NMR (400 MHz, CHLOROFORM-D) δ ppm 1.62 (s, 6 H) 2.96 (s, 3 H) 3.50 (s, 1 H) 7.62 (d, J=8.59 Hz, 2 H) 7.83 (d, J=8.79 Hz, 1 H) 7.90 (d, J=8.59 Hz, 2 H) 8.09 (dd, J=8.79, 1.76 Hz, 2 H) 8.21 (s, 1 H) 8.27 (s, 1 H); MMS [M+] cald. 327.1, found 327.0.

Example 31

4-(Hydroxymethyl)-*N*-[2-(hydroxymethyl)-1,3-benzothiazol-5-yl]benzamide

According to amide bond forming procedure described in Example 1, allyl (5-amino-1,3-benzothiazol-2-yl)methyl carbonate reacted with *p*-carboxybenzaldehyde to yield carbonic acid allyl ester 5-(4-formyl-benzoylamino)-benzothiazol-2-ylmethyl ester. This intermediate (97 mg, 0.25 mmol) and $B_{10}H_{14}$ (30 mg, 0.25 mmol) were stirred in MeOH (10. 0 mL) for 48 hours. The reaction mixture was diluted with EtOAc (40.0 mL) and water (30.0 mL) and the organic phase separated. The aqueous phase was extracted with EtOAc (2 X 10.0 mL) and the combined organic phases were washed with brine solution (30.0 mL). The organic phase was dried with Na_2SO_4, filtered and concentrated in

vacuum. The residue was purified by silica gel chromatography (1:1 EtOAc/hexanes) to yield the title product. ^{1}H NMR (400 MHz, DMSO-D6) δppm 4.56 (m, 2 H), 4.83 (m, 2 H), 5.32 (t, J=5.66 Hz, 1 H), 6.21 (t, J=5.96 Hz, 1 H), 7.45 (d, J=8.20 Hz, 2 H), 7.76 (dd, J=8.69, 1.86 Hz, 1 H), 7.94 (d, J=8.20 Hz, 2 H), 7.99 (d, J=8.59 Hz, 1 H), 8.42 (d, J=1.76 Hz, 1 H), 10.35 (s, 1 H). MS [M+H] calc. 315.1 found 315.0.

Example 32

4-*tert*-butyl-*N*-(4-cyano-2-methyl-1,3-benzothiazol-5-yl)benzamide

N-(4-Bromo-2-methyl-1,3-benzothiazol-5-yl)-4-tert-butylbenzamide (example 12) (50.0 mg, 0.124 mmol) and CuCN (22 mg, 0.248 mmol) were dissolved in DMF (3.00 mL) and heated to 250 °C in a microwave oven for 20 minutes. The mixture was cooled, and the solvent was evaporated. The residue was purified by flash chromatography on silica gel eluting with mixtures of hexanes and EtOAc (4:1, 2:1, 1:1) to yield the title product. ^{1}H NMR (400 MHz, CHLOROFORM-D) δ ppm 1.36 (s, 9 H) 2.92 (s, 3 H) 7.55 (ddd, J=8.74, 2.25, 2.10 Hz, 2 H) 7.92 (ddd, J=8.64, 2.25, 2.00 Hz, 2 H) 8.03 (d, J=8.98 Hz, 1 H) 8.58 (s, 1 H) 8.69 (m, 1H); MS [M+] calcd. 350.1, found 350.0.

Pharmacology

DRGs were dissected out from adult Sprague Dawley rats (100-300 gr), and placed on ice in L15 Leibovitz medium. The ganglia were enzyme treated with Collagenase 80U/ml+ Dispase 34 U/ml dissolved in DMEM +5% serum, overnight at 37 °C. The next day, cells were triturated with fire polished pasteur pipettes, and seeded in the center of 58 mm diameter Nunc cell dishes coated with Poly-D Lysine (1 mg/mL). The DRGs were cultured in a defined medium without foetal bovine serum, containing Dulbecco's MEM / NUT MIX F-12 (1:1) without L-glutamine but with pyridoxine, 6 mg/mL D(+)-Glucose, 100 μg/mL apo-transferrin, 1 mg/mL BSA, 20 μg/mL insulin, 2 mM L-glutamine, 50 IU/ mL Penicillin, 50 μg / mL Streptomycin and 0.01 μg/mL NGF-7S.

When the cells had grown for 2 days up to 4 weeks, the experiments were done. Cells were chosen based on size and presence of neurites. Small cells with long processes were used for recording (most likely to be C neurons, with native VR1 receptors).

The cells were recorded with conventional whole cell voltage clamp patch clamp, using the following solutions (calcium ion free):

The extracellular solution comprised (in mM): NaCl 137, KCl 5, $MgCl_2 * H_2O$ 1.2, HEPES 10, Glucose 10, EGTA 5, Sucrose 50, pH to 7.4 with NaOH.

The intracellular solution comprised K-gluconate 140, NaCl 3, $MgCl_2 * H_2O$ 1.2, HEPES 10, EGTA 1, pH to 7.2 with KOH. When the cells were penetrated with suction, a puff of capsaicin (500 nM) was used to determine if the cell expressed VR1 receptor. If not, a new cell was chosen. If yes, then the compounds were added in increasing doses before the capsaicin pulse (500 nM), to determine an IC_{50} value.

List of abbreviations

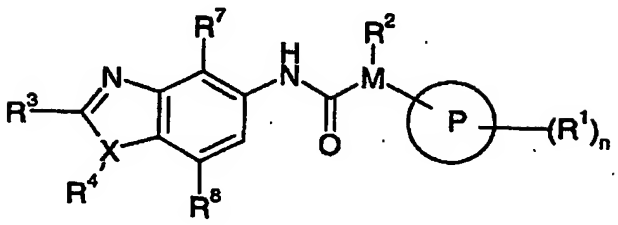
VR1	vanilloid receptor 1
IBS	irritable bowel syndrome
IBD	inflammatory bowel disease
GERD	gastro-esophageal reflux disease
DRG	Dorsal Root Ganglion
BSA	Bovine Serum Albumin
HEPES	4-(2-Hydroxyethyl)piperazine-1-ethanesulfonic acid
EGTA	Ethylene glycol-bis(2-aminoethylether)-*N,N,N',N'*-tetraacetic acid
DMEM	Dulbeccos Modified Eagle's Medium

Results

Typical IC_{50} values as measured in the assays described above are 10 μM or less. In one aspect of the invention the IC_{50} is below 500 nM. In another aspect of the invention the IC_{50} is below 100 nM. In a further aspect of the invention the IC_{50} is below 10 nM.

CLAIMS

1. A compound having the formula I



(I)

wherein:

ring P is C_{6-10}aryl, C_{3-7}cycloalkyl, C_{5-6}heteroaryl, whereby ring P may be fused with phenyl, C_{5-6}heteroaryl, C_{3-7}cycloalkyl or C_{3-7}heterocycloalkyl;

R^1 is H, NO_2, NH_2, halo, $N(C_{1-6}alkyl)_2$, C_{1-6}alkyl, C_{2-6}alkenyl, C_{2-6}alkynyl, C_{1-6}haloalkyl, C_{1-6}haloalkylO, phenylC_{0-6}alkyl, C_{5-6}heteroarylC_{0-6}alkyl, C_{3-7}cycloalkylC_{0-6}alkyl, C_{3-7}heterocycloalkylC_{0-6}alkyl, C_{1-6}alkylOC_{0-6}alkyl, C_{1-6}alkylSC_{0-6}alkyl or C_{1-6}alkylNC_{0-6}alkyl;

n is 0, 1, 2, 3 or 4;

M is H, C_{0-4}alkyl, C_{1-6}alkylNC_{0-6}alkyl, N or O;

R^2 is H or C_{0-4}alkyl;

R^3 is H, C_{1-6}alkyl, halo, C_{1-6}haloalkyl, C_{1-6}haloalkylO, C_{1-6}alkylOC_{0-6}alkyl, R^5OC_{1-6}alkyl, R^5CO, CO_2R^5, $CONR^5R^6$ or $NR^5R^6C_{0-6}$alkyl, C_{2-6}alkenylOC_{0-6}alkyl, hydroxyC_{1-6}alkyl;

X is N, O or S;

R^4 is H, C_{0-4}alkyl or hydroxyC_{1-6}alkyl;

R^5 and R^6 are independently selected from H, C_{1-6}alkyl, C_{5-6}aryl, C_{5-6}heteroaryl, SO_2C_{1-4}alkyl and COC_{1-3}alkyl;

R^7 and R^8 are independently selected from H, C_{1-6}alkyl, halo, C_{0-4}alkylcyano, C_{1-6}alkylOC_{0-6}alkyl, OH, NO_2, NH_2 andCO;

and wherein any alkyl, alkylOalkyl, haloalkyl, haloalkylO, phenyl, heteroaryl, cycloalkyl or heterocycloalkyl group may be substituted with one or more A; and

A is OH, NO_2, NH_2, CO, O(CO), halo, C_{1-6}alkylOC_{0-6}alkyl;

or salts, solvates or solvated salts thereof.

2. The compound according to claim 1 wherein wherein ring P is
C_{6-10}aryl, C_{5-6}heteroaryl, ;
R^1 is H, halo, C_{1-6}alkyl, C_{1-6}haloalkyl, C_{1-6}alkylOC_{0-6}alkyl;
n is 0, 1 or 2;
R^3 is H, C_{1-6}alkyl, halo, C_{1-6}haloalkyl, C_{1-6}haloalkylO, C_{1-6}alkylOC_{0-6}alkyl, R^5OC_{1-6}alkyl, R^5CO, CO_2R^5, $CONR^5R^6$ or $NR^5R^6C_{0-6}$alkyl, C_{2-6}alkenylOC_{0-6}alkyl, hydroxyC_{1-6}alkyl;
X is N, O or S;
R^4 is H, C_{0-4}alkyl or hydroxyC_{1-6}alkyl;
R^5 and R^6 are independently selected from H, C_{1-6}alkyl, C_{5-6}aryl, C_{5-6}heteroaryl, SO_2C_{1-4}alkyl and COC_{1-3}alkyl;
R^7 and R^8 are independently selected from C_{0-4}alkylcyano;
and wherein any alkyl, alkylOalkyl, haloalkyl, haloalkylO, phenyl, heteroaryl, cycloalkyl or heterocycloalkyl group may be substituted with one or more A; and
A is OH, NO_2, halo, C_{1-6}alkylOC_{0-6}alkyl;
or salts, solvates or solvated salts thereof.

3. The compound according to any one of claims 1 or 2 wherein ring P is phenylor pyrazole.

4. The compound according to any one of claims 1 to 3 wherein R^3 is hydroxymethyl, allyloxymethyl, ethoxymethyl, methoxypyridinylaminomethyl, pyrazolylaminomethyl, aminomethyl, methylsulfonylaminomethyl, acetylaminomethyl, carboxamide, methyl, hydroxyethyl, nitrophenylaminomethyl, hydroxycarbonyl or methoxycarbonyl.

5. The compounds selected from the group consisting of
4-tert-Butoxy-N-[2-(hydroxymethyl)-1,3-benzothiazol-5-yl]benzamide,
4-Bromo-N-[2-(hydroxymethyl)-1,3-benzothiazol-5-yl]benzamide,
N-[2-(Hydroxymethyl)-1,3-benzothiazol-5-yl]-4-iodobenzamide,
N-[2-(Hydroxymethyl)-1,3-benzothiazol-5-yl]-4-morpholin-4-ylbenzamide,

N-{2-[(Allyloxy)methyl]-1,3-benzothiazol-5-yl}-4-morpholin-4-ylbenzamide,
N-[2-(Hydroxymethyl)-1,3-benzothiazol-5-yl]-1-phenyl-5-propyl-1H-pyrazole-4-carboxamide,
1-tert-Butyl-N-[2-(hydroxymethyl)-1,3-benzothiazol-5-yl]-3-methyl-1H-pyrazole-5-carboxamide,
4-(Ethoxymethyl)-N-[2-(hydroxymethyl)-1,3-benzothiazol-5-yl]benzamide,
N-[2-(Hydroxymethyl)-1,3-benzothiazol-5-yl]-1-phenyl-1H-pyrazole-5-carboxamide,
4-Bromo-N-[2-(hydroxymethyl)-1,3-benzothiazol-5-yl]-2-methylbenzamide,
4-tert-Butoxy-N-(2-methyl-1,3-benzoxazol-5-yl) benzamide,
N-(4-Bromo-2-methyl-1,3-benzothiazol-5-yl)-4-tert-butylbenzamide,
4-tert-Butyl-N-(4,7-dibromo-2-methyl-1,3-benzothiazol-5-yl)benzamide,
N-[2-(hydroxymethyl)-1,3-benzothiazol-5-yl]-1-phenyl-5-(trifluoromethyl)-1H-pyrazole-4-carboxamide,
4-Iodo-N-(2-methyl-5-benzothiazolyl)benzamide,
4-(tert-Butoxymethyl)-N-[2-(hydroxymethyl)-1,3-benzothiazol-5-yl]benzamide,
N-(1,2-Dimethyl-1H-benzimidazol-5-yl)-4-iodobenzamide,
4-tert-Butyl-N-(2-{[(2-methoxypyridin-3-yl)amino]methyl}-1,3-benzothiazol-5-yl)benzamide,
4-tert-Butyl-N-[2-(1-hydroxyethyl)-1,3-benzothiazol-5-yl]benzamide,
4-tert-Butyl-N-{2-[(1H-pyrazol-3-ylamino)methyl]-1,3-benzothiazol-5-yl}benzamide,
4-(1,1-Dimethylethyl)-N-[2-[[(4-nitrophenyl)amino]methyl]-5-benzothiazolyl]-benzamide ,
N-[2-(Aminomethyl)-1,3-benzothiazol-5-yl]-4-tert-butylbenzamide,
4-tert-Butyl-N-(2-{[(methylsulfonyl)amino]methyl}-1,3-benzothiazol-5-yl)benzamide,
N-{2-[(Acetylamino)methyl]-1,3-benzothiazol-5-yl}-4-tert-butylbenzamide,
5-[(4-tert-Butylbenzoyl)amino]-1,3-benzothiazole-2-carboxamide,
N-1,3-Benzothiazol-5-yl-4-tert-butylbenzamide,
4-Chloro-N-[2-(hydroxymethyl)-1,3-benzothiazol-5-yl]benzamide,
1-(4-chlorophenyl)-N-[2-(hydroxymethyl)-1,3-benzothiazol-5-yl]-5-propyl-1H-pyrazole-4-carboxamide,
1-(4-chlorophenyl)-N-[2-(hydroxymethyl)-1,3-benzothiazol-5-yl]-5-(trifluoromethyl)-1H-pyrazole-4-carboxamide,
N-(2,4-dimethyl-1,3-benzothiazol-5-yl)-4-(1-hydroxy-1-methylethyl)benzamide,
4-(Hydroxymethyl)-N-[2-(hydroxymethyl)-1,3-benzothiazol-5-yl]benzamide and

4-tert-butyl-N-(4-cyano-2-methyl-1,3-benzothiazol-5-yl)benzamide,
or salts, solvates or solvated salts thereof.

6. The compound according to any one of claims 1 to 5, for use in therapy.

7. Use of the compound according to any one of claims 1 to 5, in treatment of VR1 mediated disorders.

8. The use according to claim 7 for treatment of acute and chronic pain disorders.

9. The use according to claim 7 for treatment of acute and chronic inflammatory pain.

10. The use according to claim 7 for treatment of indications selected form the group consisting of arthritis, fibromyalgia, low back pain, post-operative pain, visceral pains like chronic pelvic pain, cystitis, IBS, pancreatitis, sciatia, diabetic neuropathy, HIV neuropathy, asthma, cough, IBD, psoriasis, gastro-esophageal reflux disease (GERD), emesis, urinary incontinence and hyperactive bladder.

11. Use of the compound of formula I according to any one of claims 1 to 5, in the manufacture of a medicament for the treatment of VR1 mediated disorders and for the treatment of acute and chronic pain disorders and acute and chronic inflammatory pain.

12. A method of treatment of VR1 mediated disorders and for treatment of acute and chronic pain disorders and acute and chronic inflammatory pain, comprising administrering to a mammal, including man in need of such treatment, a therapeutically effective amount of the compound of formula I, according to any one of claims 1 to 5.

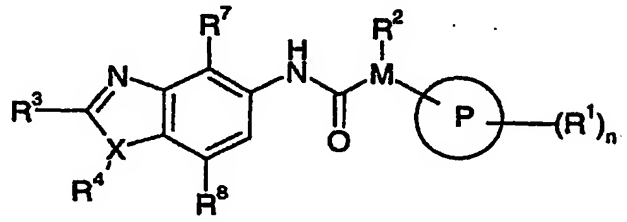
13. A pharmaceutical formulation comprising as active ingredient a therapeutically effective amount of the compound of formula I, according to any one of claims 1 to 5, in association with one or more pharmaceutically acceptable diluents, excipients and/or inert carriers.

14. The pharmaceutical formulation according to claim 13, for use in the treatment of VR1 mediated disorders and for treatment of acute and chronic pain disorders and acute and chronic inflammatory pain.

15. Use of compounds allyl (5-amino-1,3-benzothiazol-2-yl)methyl carbonate, 4-tert-Butyl-N-(2-formyl-1,3-benzothiazol-5-yl)-benzamide, and 4-Bromo-2-methyl-benzothiazol-5-ylamine as intermediates in the preparation of the compound of formula I.

ABSTRACT

The present invention relates to new compounds of formula I,



(I)

wherein R^1 to R^8 are as defined as in formula I, or salts, solvates or solvated salts thereof, processes for their preparation and to new intermediates used in the preparation thereof, pharmaceutical formulations containing said compounds and to the use of said compounds in therapy.

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